Nutriepigenomics: The role of nutrition in epigenetic control of human diseases

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REVIEW

Nutriepigenomics: the role of nutrition in epigenetic control of human diseases

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Purpose of review
Nutrients or even diets affect the epigenome by lifelong remodeling. Nutritional imbalances are associated with noncommunicable diseases. Thus, nutriepigenomics is a promising field in the treatment of complex human diseases.

Recent findings
The epigenome is susceptible to changes and can be shaped by nutritional states, especially in prenatal period through transgenerational mechanisms and in early postnatal life when critical developmental processes are taking place. Although more stable, the epigenetic marks in adulthood are also dynamic and modifiable by environmental factors including diet.

Summary
The present review is focused on the most recent knowledge of epigenetically active nutrients/diets including transgenerational inheritance and prenatal predispositions related to increased risk for cancer, metabolic syndrome, and neurodegenerative diseases.

Keywords
adulthood, postnatal, prenatal, transgenerational effects

INTRODUCTION

Nutrition, the intake of food, influences all processes essential for the maintenance of life and health, for example, body heat, muscle activity, growth, and immunity [1]. Conventional, nutritional research focuses on guidelines of sufficient daily intake of nutrients to prevent deficiencies and to promote human health, although complex diseases are not only a result of insufficient nutrient uptake or the lack of energy expenditure but also depend on the interaction of nutrients with DNA. The term 'nutriepigenomics' describes these interactions, meaning the study of nutrients and their effects on human health through epigenetic modifications defined as stable heritable patterns of gene expression occurring without changes in the DNA sequence [2]. These epigenetic patterns include interacting components at transcriptional level, DNA methylation and histone modifications, and at the post-transcriptional level, RNA interference [3–6]. In addition, to the nutrition of an individual, we have to consider also transgenerational, prenatal, and postnatal effects as epigenetic alterations at critical time points during development can result in stable changes and predispose individuals to disease later in life [7]. Numerous non-Mendelian features of metabolic syndrome, cancer, or central nervous system disorders, clinical differences between men and women or monozygotic twins are associated with epigenetic effects of fetal and/or lifelong nutrition [8]. One famous example of nutriepigenomics is the development of a honeybee into a queen or worker with identical genomes following different feeding with royal jelly or a diet of pollen and nectar, respectively [9].

Nutrients affecting one of the two metabolites of the 1-carbon metabolism, S-adenosylmethionine,

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KEY POINTS

- The action of many bioactive substances is specific to enzymes and proteins involved in the regulation of different components of the epigenome, interaction with other nutrients and lifestyle factors in physiological and pathological conditions must be taken into account, as well.
- In addition, to the nutrition of an individual, we have to consider also transgenerational, prenatal, and postnatal effects as epigenetic alterations in critical time points during development can result in stable changes and predispose individuals to disease.
- Transgenerational epigenetic inheritance can result from a variety of environmental manipulations in either parent, although little is known about the duration of maintenance.
- ~~'Early life programming' terms~~ the phenomenon of prenatal and early-postnatal influences, for example, nutrition, to certain diseases later in life.
- Although more stable, the epigenetic marks in adulthood are also dynamic and modifiable by environmental factors including diet.

an ubiquitous methyl donor, or S-adenosylhomocysteine, an inhibitor of methyltransferases, potentially alter the methylation of DNA and histones. Methylated promoter and other regulatory regions of a gene are usually associated with gene repression, whereas DNA demethylation within these regions leads to gene activation [2]. Polyphenols, including curcumin, genistein, epigallocatechin gallate (EGCG), resveratrol, and equol, are well known for their beneficial effects via modulation of nuclear factor kappa B (NF-κB) expression, chromatin remodeling through regulation of histone deacetylase (HDAC), and DNA methyltransferase activities. Components such as gut microbial derived butyrate, sulforaphane, and curcumin affect histone acety transferase (HAT) and/or HDAC activities leading to changes in chromatin structure. Vitamins like biotin, niacin, and pantothenic acid, influence histone modifications, for example, biotin influences histone biotinylation and niacin histone ADP-ribosylation. Resveratrol, butyrate, sulforaphane, and diallyl sulfide inhibit HDACs, whereas curcumin inhibits HATs [4]. Although the action of many bioactive substances is specific to enzymes and proteins involved in the regulation of different components of the epigenome, interaction with other nutrients and lifestyle factors in physiological and pathological conditions must be taken into account as well [4]. In addition, epigenetic components exert effect over each other. It adds an additional layer of complexity to the action of epigenetically active nutrients. Studies demonstrate that DNA methylation and histone modifications that act together to establish chromatin structure are involved in miRNA regulation and vice versa [10]. Thus, deeper knowledge of bioactive nutrients/diets for characterization of their effects on the epigenome modifying enzymatic activities (acetylation, methylation, phosphorylation, ribosylation, oxidation, ubiquitination, and sumoylation) influencing drug absorption, distribution, metabolism, and excretion is needed [4].

The present review summarizes the most recent knowledge of epigenetic active nutrients/diets in regard to their role in the epigenetic control of human diseases focusing on three of the worldwide most common disorders: cancer, metabolic syndrome, and neurodegenerative diseases (Table 1) [11–15,16▪▪,17,18▪–20▪,21,22,23▪,24▪,25,26].

TRANSGENERATIONAL EFFECTS

The belief of a wiped epigenetically clean embryo shortly after fertilization is recently disproved by the discovery of transgenerational effects. This transgenerational inheritance is due to incorrect deletion of epigenetic marks generated by the behavior and nutrition of previous generations [27]. After fertilization, the global DNA methylation is suggested to be deleted [28▪], ~~either~~ the regulation of histone modifications is rather unknown. Studies on 'the Dutch famine of 1944' increased the evidence of transgenerational inheritance, starvation in one generation affects the health of the grandchildren [29].

Postnatal maternal care or maternal separation induced depressive-like behavior or increased risk-taking behavior in two generations of the offspring through increased DNA methylation of the chromatin regulator methyl cytosine-guanine dinucleotide (CpG) binding protein 2 together with a decreased methylation status of a stress hormone receptor, the corticotropin releasing factor receptor 2 [11]. Influencing factors like nutritional interventions (caloric restriction or fat-rich or carbohydrate-rich diet), endocrine disruptors, maternal diabetes, behavioral programming (maternal care), glucocorticoids and exercise, stress during pregnancy and lactation may all cause imprinting in the following generation(s) [30]. Implication of the F3 generation is rare and reported results are conflicting [31]. Transmission down the female line is reproducible as one generation resides inside another generating a cascade of transplacental metabolic effects down the generations, although little is known about imprint establishment or deletion from a father and implication

Table 1. Influencing factors and their effects

Influencing factors	Model	Effects	Reference
Transgenerational effects			
postnatal maternal care or maternal separation	mice	depressive-like behavior or increased risk-taking behavior in two generations through DNA increased methylation of MeCP2, decreased methylation of CRFR2	[11]
overeating of the paternal grandfather or father	human	higher risk for cardiovascular diseases or diabetes	[12]
restricted food availability during father's slow growth period	human	reduced cardiovascular risk in offsprings	[12]
Prenatal–Postnatal			
Maternal protein malnutrition	mice	hypomethylation of the CpG islands in the promoter regions of ACE-1	[13]
decreased nutrient intake of the mother	humans	reduction in methylation of IGF2R in girls and GTL2-2 in boys	[14,15]
poor prenatal nutrition	humans	fetal growth restriction, LBW, postnatal reproductive dysfunction and poor pregnancy outcomes	[16▪▪]
intrauterine growth restriction during the pregnancy	humans	downregulation of DNA methylation in the HNF4a gene of blood stem cell	[17]
alcohol consume during pregnancy	humans	hypermethylation of POMP promoter	[18▪,19▪]
breastfeeding	rats	higher plasma cholesterol and lower HDL values	[20▪]
Adulthood			
annurca apple in the diet	mice, human colorectal cancer cell lines	lower incidence of colorectal cancer; activation of methylation-silenced tumor suppressor genes	[21]
apple extract supplementation (chlorogenic acid, phloridzin, quercetin, catechin, epicatechin, procyandiin, rutin)	rats	decreased methylation in leptin promoter region, body weight gain prevention and improved hyperglycemia, hyperleptinemia, and insulin resistance	[22]
pill combining four foods: pomegranate, green tea, turmeric, broccoli	humans	decrease in markers of prostate cancer	[23▪]
coffee consumption	humans	decreased risk of liver cirrhosis and hepatocellular carcinoma	[24▪,25]
supplementation with resveratrol	humans	improved metabolic functions	[26]

ACE-1, angiotensin converting enzyme-1; CpG, cytosine-guanine dinucleotide; CRFR2, corticotropin releasing factor receptor 2; GTL2-2, Gon-Two Like; HDL, high density lipoprotein; HNF4a, hepatocyte nuclear factor 4 alpha; IGF2R, insulin-like growth factor 2 receptor; LBW, low-birth weight; MeCP2, methyl CpG binding protein 2; POMP, proteasome maturation protein.

of epigenetic marks in sperm DNA are suggested. Evidence arises from a study conducted in Överkalix in 1890, 1905, and 1920 up until death or 1995. Overeating by the paternal grandfather or of the father induced higher risk for cardiovascular diseases or diabetes, whereas restricted food availability during the father's slow growth period reduced the cardiovascular risk in the offspring. The results suggest early adolescence as an important period for nutrient response in ways that potentially affect future generations [12]. Thus, transgenerational epigenetic inheritance can result from a variety of environmental manipulations in either parent with a possible evolutionary advantageous but also erroneous transmission. Although little is known about the duration of maintenance and how the marks and signals are deleted or reset as well as how many generations the epigenetically inherited phenotype lasts.

PRENATAL: POSTNATAL

Although the prenatal period and adulthood are very distant from each other, there is an important correlation between those two key phases in life. More and more evidence is accumulating, pointing to the important fact that prenatal and early-postnatal nutrition plays a critical role in determining susceptibility to certain diseases later in life. This phenomenon was termed as 'early-life programming' [32▪]. Substantial indications for this theory are collected in the field of metabolic diseases, such as obesity, dyslipidemia, hypertension, hyperinsulinemia, taken together as metabolic syndrome, as

well as in the field of cardiovascular diseases [33]. There are some hypotheses trying to explain this connection between early-life circumstances and the incidence of maladies in adulthood. One idea proposes that there is an association between poor growth *in utero* and in infancy, and a higher risk of developing metabolic syndrome in adulthood as discovered in epidemiological research. This might be explained easily by the idea of 'thrifty phenotype hypothesis' – metabolic homeostasis is disrupted due to a poor nutrient availability later in life leading to the presence of metabolic disease [34]. Current research in animal models demonstrates that early inadequate nutrition, including parental conditions, lifestyle, nutritional supplements, therapeutically potent substances, not to forget psychological stress, probably alter specific processes through epigenetic marks with lifelong influence on distinct functions [35,13]. For example, it has been shown in mice that protein malnutrition in pregnant mice causes significant gene expression changes, miRNA changes, and different DNA methylation patterns in brains of the offspring [13]. Moreover, there has been evidence showing, that a maternal high-fat diet influences specific epigenetic mechanisms in fetal epigenome [36]. Another fact comes from human study in which the authors have shown that administration of folic acid before and during pregnancy is related to increased methylation at differentially methylated region of insulin-like growth factor 2 (IGF2) in the child [37]. Even some micronutrients have been shown to importantly influence early epigenetic status. For example, vitamin B12, B6, B2, choline, betaine, and methionine are all involved in maintenance of DNA methylation signatures. The availability through maternal diet has been shown to directly influence not only gene expression, but have an effect on the infants' phenotype, as well. Adult offspring were heavier and had a higher fat content, also displaying insulin resistance and elevated blood pressure. Their immune response was significantly altered, as well [4]. Another example of the effects of decreased nutrient intake during gestation is shown in the epidemiological studies in Gambia. They suggest a correlation between the reduction of micronutrients during preconception and the phenotype of the offspring. This malnourishment leads to a reduction in methylation in two regions in a sex-specific manner, namely IGF2 receptor in girls and Gon-Two Like 2 in boys. These genes have an important role in the regulation of blood glucose levels and in the growth, respectively [14,15]. The cell population in which equilibrium of nutrients is crucial is the stem cell population. Current research suggests that early-life events such as poor prenatal nutrition have significant effects on the reproductive maturation of the offspring leading to maladies such as fetal growth restriction, low-birth weight, postnatal reproductive dysfunction and poor pregnancy outcomes and may even contribute to early aging and menopause [16▪▪]. Complementing these results is the study of Einstein *et al.* [17], suggesting that dysregulation of DNA methylation in the hepatocyte nuclear factor 4, alpha gene in the blood stem cell population [CD34 (cluster of differentiation) positive cells] is a result of intrauterine growth restriction. Another factor that plays a role during embryogenesis is consumption of alcohol by the mother during pregnancy that can lead to so called fetal alcohol spectrum disorder (FASD). Prenatal exposure to alcohol epigenetically modulates proteasome maturation protein neurons, which are essential in the control of adult behavior. Identifying the epigenetic mechanisms controlling these neurons would be of great importance [18▪,19▪]. The fact that breastfeeding is beneficial for the offspring is well established. Research in rats has demonstrated that early weaning increases plasma cholesterol and decreases high density lipoprotein values. These results confirm that the mother's milk is essential for the offspring's ability to encounter and overcome nutritional irregularities later in life [20▪].

ADULTHOOD

Aberrations in the epigenome during development and early life play a role in genome adaptation to external stimuli, and if they persist, they may result in adverse effects and disease later in life. However, reversibility of altered gene expression has been demonstrated not only during development but also later in adulthood. Exposure to environmental cues such as diet can result in changes in the epigenome and specifically the methylome (DNA methylation patterns), which alters gene expression profiles and other genome functions, leading to prevention of health deterioration with existing evidence in cancer, metabolic syndrome, and neurodegenerative diseases. Lower incidence of colon inflammation, which is considered as an initial step leading to colorectal cancer, has been linked to the presence of Annurca apple in the diet in the population of southern Italy in comparison with the rest of the Western world [21]. Purified polyphenols such as resveratrol, genistein, and EGCG present in grapes, soybeans, and green tea, respectively, were also shown to reverse DNA methylation-mediated silencing of tumor suppressor genes in many cancer types that resulted in decreased uncontrolled cell growth [38,39]. A dietary supplementation with

apple extracts (chlorogenic acid, phloridzin, quercetin, catechin, epicatechin, procyandiin, rutin) decreased the methylation of two CpG sites in the leptin promoter resulting in body weight gain prevention and improved hyperglycemia, hyperleptinemia, and insulin resistance [22]. An increase in leptin production can be also induced by short chain fatty acids (SCFAs) together with higher expression of free fatty acid receptor 3 [40▪], indicating that supplementation with SCFAs or nutritional interventions stimulating gut microbial butyrate producers might help to improve the sensitivity or the production of leptin [41]. A combination of four foods rich in polyphenols, pomegranate (ellagitannins), green tea (catechins), turmeric (curcumin), and broccoli (sulforaphane), concentrated into a pill, decreased markers of prostate cancer growth by a median of nearly 64% in double-blind placebo-controlled randomized trial [23▪]. All four polyphenols have been demonstrated in multiple in-vitro and/or in-vivo studies to affect all three components of the epigenome, DNA methylation, histone marks, and microRNAs [42–45]. Several studies consistently show that coffee drinkers with chronic liver disease have a reduced risk of cirrhosis and a substantially lower incidence of hepatocellular carcinoma regardless of primary cause [24▪]. Furthermore, coffee drinkers have 13–18% lower overall risk of cancers [25]. As health impacts of caffeinated and decaffeinated coffee are similar, anticancer effects of coffee appear to be related to polyphenols, such as chlorogenic acid and caffeic acid. Both compounds are excellent substrates for catechol-O-methyltransferase, which affects the pool of methyl donors in a cell and subsequently changes epigenetic methyl marks in DNA [46]. Polyphenols also exert beneficial effects in metabolic disorders through activating AMPK–SIRT1–PGC1alpha axis, which was shown in obese individuals. PGC1alpha is crucial for mitochondrial function and is controlled by epigenetic mechanisms [26]. Gut microbiota is also known for an aberrant composition, for example, increased *Firmicutes/Bacteroidetes* ratio, due to metabolic syndrome, Western diet, with a possible influence on methylation patterns of Toll-like receptor (TLR) 2 and TLR4 affecting NFκ-B, low-grade inflammation [40▪].

CONCLUSION

In conclusion, it is evident that nutrients and bioactive food components interact with the genome through epigenetic alterations leading to different gene expression patterns. Thus, different epigenetic patterns provide information on dietary habits but also on the prospect of optimized dietary interventions for prevention and therapy in numerous diseases.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ▪ of special interest
- ▪▪ of outstanding interest

1. WorldHealthOrganization(WHO). Nutrition. WHO; 2014 [Adapted on 22 October 2014]; Available from: http://www.who.int/topics/nutrition/en/.
2. Tammen SA, Friso S, Choi SW. Epigenetics: the link between nature and nurture. Mol Aspects Med 2013; 34:753–764.
3. Oliver SS, Denu JM. Dynamic interplay between histone H3 modifications and protein interpreters: emerging evidence for a ''histone language''. Chem biochem 2011; 12:299–307.
4. Choi SW, Friso S. Epigenetics: a new bridge between nutrition and health. Adv Nutr 2010; 1:8–16.
5. Jimenez-Chillaron JC, Diaz R, Martinez D, *et al.* The role of nutrition on epigenetic modifications and their implications on health. Biochimie 2012; 94:2242–2263.
6. Sawicka A, Seiser C. Histone H3 phosphorylation: a versatile chromatin modification for different occasions. Biochimie 2012; 94:2193–2201.
7. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol 2011; 31:363–373.
8. Vanden Berghe W. Epigenetic impact of dietary polyphenols in cancer chemoprevention: Lifelong remodeling of our epigenomes. Pharmacol Res 2012; 65:565–576.
9. Chittka A, Chittka L. Epigenetics of royalty. PLoS Biol 2010; 8:e1000532.
10. Su Z, Xia J, Zhao Z. Functional complementation between transcriptional methylation regulation and posttranscriptional microRNA regulation in the human genome. BMC Genom 2011; 12 (Suppl 5):S15.
11. Franklin TB, Russig H, Weiss IC, *et al.* Epigenetic transmission of the impact of early stress across generations. Biol Psychiatry 2010; 68:408–415.
12. Kaati G, Bygren LO, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Eur J Hum Genet 2002; 10:682–688.
13. Goyal R, Goyal D, Leitzke A, *et al.* Brain renin-angiotensin system: fetal epigenetic programming by maternal protein restriction during pregnancy. Reprod Sci 2010; 17:227–238.
14. Cooper WN, Khulan B, Owens S, *et al.* DNA methylation profiling at imprinted loci after periconceptional micronutrient supplementation in humans: results of a pilot randomized controlled trial. FASEB J 2012; 26:1782–1790.
15. Khulan B, Cooper WN, Skinner BM, *et al.* Periconceptional maternal micronutrient supplementation is associated with widespread gender related changes in the epigenome: a study of a unique resource in the Gambia. Hum Mol Genet 2012; 21:2086–2101.
16. ▪▪ Chan KA, Tsoulis MW, Sloboda DM. Early life nutritional effects on the female reproductive system. J Endocrinol 2015; 224:R45–R62.
It links the early-life developmental environment and postnatal reproductive development.
17. Einstein F, Thompson RF, Bhagat TD, *et al.* Cytosine methylation dysregulation in neonates following intrauterine growth restriction. PloS One 2010; 5:e8887.
18. ▪ Young JK, Giesbrecht HE, Eskin MN, *et al.* Nutrition Implications for Fetal Alcohol Spectrum Disorder. Advanc Nutr 2014; 5:675–692.
This research illuminates the connections between maternal abundance of nutrients and their inhibitory effect on the development of FASD.
19. ▪ Bekdash R, Zhang C, Sarkar D. Fetal alcohol programming of hypothalamic proopiomelanocortin system by epigenetic mechanisms and later life vulnerability to stress. Alcohol Clin Exp Res 2014; 38:2323–2330.
Yield useful new therapeutic targets to treat stress-related maladies in patients with fetal alcohol spectrum disorders.

20. Carvalho JC, de Oliveira E, Peixoto-Silva N, *et al.* Maternal prolactin inhibition
■ causes changes in leptin at 22- and 30-day-old pups. Horm Metab Res et metabolisme 2014.
Proofing that breastfeeding exerts a crucial role in the survival adaptation to adverse nutritional conditions.
21. Fini L, Piazzi G, Daoud Y, *et al.* Chemoprevention of intestinal polyps in ApcMin/+ mice fed with western or balanced diets by drinking annurca apple polyphenol extract. Cancer Prev Res (Phila) 2011; 4:907–915.
22. Boque N, de la Iglesia R, de la Garza AL, *et al.* Prevention of diet-induced obesity by apple polyphenols in Wistar rats through regulation of adipocyte gene expression and DNA methylation patterns. Mol Nutr Food Res 2013; 57:1473–1478.
23. Thomas R, Williams M, Sharma H, *et al.* A double-blind, placebo-controlled
■ randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer–the U.K. NCRN Pomi-T study. Prostate Cancer Prostatic 2014; 17:180–186.
This publication shows that food rich in polyphenols has an inhibiting effect on primary systemic amyloidosis.
24. Chen S, Teoh NC, Chitturi S, Farrell GC. Coffee and nonalcoholic fatty liver
■ disease: brewing evidence for hepatoprotection? J GastroenterolHepatol 2014; 29:435–441.
Show new insights into the hepatoprotective effects of coffee.
25. Yu X, Bao Z, Zou J, Dong J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer 2011; 11:96.
26. Timmers S, Konings E, Bilet L, *et al.* Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metabol 2011; 14:612–622.
27. Daxinger L, Whitelaw E. Transgenerational epigenetic inheritance: more questions than answers. Genome Res 2010; 20:1623–1628.
28. Messerschmidt DM, Knowles BB, Solter D. DNA methylation dynamics during
■ epigenetic reprogramming in the germline and preimplantation embryos. Genes Dev 2014; 28:812–828.
Global DNA methylation is affected after fertilization due to epigenetic reprogramming.
29. Lumey LH. Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944-1945. Paediatr Perinat Epidemiol 1992; 6:240–253.
30. Rahman I, Bagchi D, editors. Inflammation, Advancing Age and Nutrition: Research and Clinical Interventions; 2013.
31. Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2005; 288:R34–R38.
32. Mathias PC, Elmhiri G, de Oliveira JC, *et al.* Maternal diet, bioactive molecules
■ and exercising as reprogramming tools of metabolic programming. Eur J Nutr 2014; 53:711–722.
Crucial research terming the phrase 'early-life programming'.
33. Lillycrop KA. Effect of maternal diet on the epigenome: implications for human metabolic disease. Proc Nutr Soc 2011; 70:64–72.
34. Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull 2001; 60:5–20.
35. Campion J, Milagro F, Martinez JA. Epigenetics and obesity. Prog Mol Biol Transl Sci 2010; 94:291–347.
36. Heerwagen MJ, Miller MR, Barbour LA, Friedman JE. Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. Am J Physiol Regul Integr Comp Physiol 2010; 299:R711–R722.
37. Hoyo C, Murtha AP, Schildkraut JM, *et al.* Methylation variation at IGF2 differentially methylated regions and maternal folic acid use before and during pregnancy. Epigenetics 2011; 6:928–936.
38. Stefanska B, Rudnicka K, Bednarek A, Fabianowska-Majewska K. Hypomethylation and induction of retinoic acid receptor beta 2 by concurrent action of adenosine analogues and natural compounds in breast cancer cells. Eur J Pharmacol 2010; 638:47–53.
39. Stefanska B, Salame P, Bednarek A, Fabianowska-Majewska K. Comparative effects of retinoic acid, vitamin D and resveratrol alone and in combination with adenosine analogues on methylation and expression of phosphatase and tensin homologue tumour suppressor gene in breast cancer cells. Br J Nutr 2012; 107:781–790.
40. Remely M, Aumueller E, Jahn D, *et al.* Microbiota and epigenetic regulation of
■ inflammatory mediators in type 2 diabetes and obesity. Benef Microbes 2014; 5:33–43.
The influence of gut microbiota on epigenetic regulation of inflammatory mediators.
41. Remely M, Aumueller E, Merold C, *et al.* Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene 2013; 537:85–92.
42. Khor TO, Huang Y, Wu TY, *et al.* Pharmacodynamics of curcumin as DNA hypomethylation agent in restoring the expression of Nrf2 via promoter CpGs demethylation. Biochem Pharmacol 2011; 82:1073–1078.
43. Wong CP, Hsu A, Buchanan A, *et al.* Effects of sulforaphane and 3,3'-diindolylmethane on genome-wide promoter methylation in normal prostate epithelial cells and prostate cancer cells. PloS one 2014; 9: e86787.
44. Banerjee N, Kim H, Talcott S, Mertens-Talcott S. Pomegranate polyphenolics suppressed azoxymethane-induced colorectal aberrant crypt foci and inflammation: possible role of miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR. Carcinogenesis 2013; 34:2814–2822.
45. Stefanska B, Karlic H, Varga F, *et al.* Epigenetic mechanisms in anticancer actions of bioactive food components: the implications in cancer prevention. Br J Pharmacol 2012; 167:279–297.
46. Rajavelu A, Tulyasheva Z, Jaiswal R, *et al.* The inhibition of the mammalian DNA methyltransferase 3a (Dnmt3a) by dietary black tea and coffee polyphenols. BMC Biochem 2011; 12:16.